Dry antibiotic pipeline: Regulatory bottlenecks and regulatory reforms

Sandeep Kumar Gupta, Roopa P. Nayak

Department of Pharmacology, Dhanalakshmi Srinivasan Medical College and Hospital, Siruvachur, Perambalur, Tamil Nadu, India

INTRODUCTION

Only 2 new classes of antibiotics have emerged in the past 3 decades, namely, oxazolidinones (linezolid) and cyclic lipopeptides (daptomycin).[1] The antibacterial pipeline is scarce because of the costs associated with the development and licensure of antibiotics and the complexity of conducting clinical trials.[2] Recruitment and enrollment of an adequate number of patients in clinical trials for novel antibacterial remain very challenging and costly. In addition, no one can cut corners on safety. The US FDA has recently issued a draft guidance on scientific justification of margins in non-inferiority trials for treatments of acute bacterial skin and skin structure infections. The US FDA has also required superiority trials for antibiotics used to treat self-resolving nonlethal infections. This would increase the number of patients to be enrolled in antibiotic trials, and thus, increase the trial expenditure.[3] In this article, we attempt to discuss various regulatory bottlenecks in the development of novel antibacterial drugs. In the latter part of the article, we discuss various regulatory reforms that could improve novel antibacterial development.

REGULATORY BOTTLENECKS

At present, clinical trials involving novel antibiotics face multiple regulatory bottlenecks, which are mentioned below:[2,4-6]

Access this article online	
Quick Response Code:	Website: www.jpharmacol.com
	DOI: 10.4103/0976-500X.124405

- Demanding phase III study protocols
- Necessity for all licensed indications to be microbiologically documented
- Increased stringency of safety requirements for pre-licensing and post-licensing procedures (despite these stringent requirements, risk/benefit definition remains unclear)
- Higher standards for efficacy and safety trials
- Prolonged evaluation/decision time that affects return on investment (ROI)
- Regulatory stringency coupled with bureaucratic hurdles
- Failure of harmonization of international regulatory requirements; and
- Slow updating of guidelines.

Regulatory reforms

The US FDA (Innovation or Stagnation: Challenge and Opportunity on the Critical Path to New Medical Products), Infectious Diseases Society of America (IDSA), British Society for Antimicrobial Chemotherapy (BSAC), and the California Healthcare Institute have suggested the following specific reforms that would improve both the development of critical antibacterial agents and the regulatory review process in entirety.[5-9]

Consideration of preclinical and clinical data for approval

Demonstrable efficacy in animal models and secondary clinical outcomes such as bacterial eradication together with a single well-designed phase 3 trial should be considered sufficient for review of drug approval.[8]

Adaptive clinical trial design

Because the clinical trials that evaluate antibiotic efficacy against resistant bacteria are time-consuming and costly, the US FDA has suggested the use of adaptive clinical trial designs. Patient cohorts consistent with the frequency and severity of

Address for correspondence:
Sandeep Kumar Gupta, Department of Pharmacology, Dhanalakshmi Srinivasan Medical College and Hospital, Siruvachur, Perambalur - 621 113, Tamil Nadu, India. E-mail: drsandeep_gupta@rediffmail.com

the disease should be included in the trials for approval. The requirement that patients infected with resistant organisms be excluded from the analysis of the control group but not the experimental group should be eliminated by the regulatory agency.[6,8]

Placebo-controlled trials to evaluate antibiotic therapy

National Institute of Allergy and Infectious Diseases (NIAID) has suggested that placebo-controlled trials should be funded to evaluate the necessity of antibiotic therapy for specific diseases. Antibiotics are very commonly prescribed to treat diseases that are not caused by bacteria (e.g., virus), and this may lead to antibiotic resistance with no benefit to the patients. Hence, definitive placebo-controlled studies would be required to elaborate the necessity of antibiotic therapy for specific diseases.[6]

Relaxed standards for demonstrating equivalence to the active comparator

Broadly, there are 4 kinds of controlled trials that provide efficacy evidence. Among them, placebo, no treatment, and dose-response controlled trials are superiority trials. The purpose of a superiority trial is to show that a test drug is superior to the control, e.g., placebo, no treatment, or a lower dose of the test drug. The fourth type of controlled trial involves comparison with an active treatment (active control); this type of trial demonstrates superiority or noninferiority of the test drug to the active drug. In the case of a noninferiority clinical trial, the purpose is to show that test product is not inferior to the comparator by more than a specified, small amount known as delta, which has previously been determined in a placebo-controlled trial of the comparator drug. The standard delta value for most antibiotic trials is 15%.[3,10]

Most clinical trials involving antibiotics are active-controlled, noninferiority trials. The US FDA has recently drafted guidelines for noninferiority margins for trials on acute bacterial skin infections and other skin infections. These guidelines have proposed the use of narrower efficacy margins, which tend to increase the number of patients involved and the trial cost. However, such an increase in the number of study patients seems to be unfeasible from a clinical standpoint for not-so-common but important infectious diseases. It may also culminate in the trial becoming so lengthy that the comparator drug may no longer be considered appropriate due to the emergence of antibiotic resistance.[1-4]

The results of a superiority trial are easily decipherable; however, noninferiority trials suffer the criticism of not being able to record assay sensitivity, which is essential for understanding the results. The International Conference on Harmonization (ICH) E10 defines assay sensitivity as the property of a clinical trial that distinguishes an effective treatment from a less effective or ineffective treatment. Thus, if the active control shows no effect at all in the noninferiority trial, even a very small difference between the control and the test drug is futile because it does not correspond to efficacy of the test drug. Thus, the likelihood of inadequate efficacy may be reduced if the regulatory agency specifies an appropriate antibiotic comparator for each indication.[2,3,10,11]

Allowing pooling of trial data of different indications for uncommon conditions

Pooling of data on the efficacy of a drug against indications other than that under investigation (infection due to uncommon resistant pathogens) should be permitted by the regulatory agency. This would allow the selection of an agent that is effective against multidrug-resistant organisms in specific clinical contexts.[8]

Accelerated approval for targeted indications

Expediting the review of new drug applications can shorten the drug approval time by the regulatory agency. The regulatory agency might approve the application for a new drug (NDA) or a biological (BLA) product on the basis of the results of an efficacy trial involving a surrogate endpoint. The accelerated approval process may then depend on the confirmatory studies conducted in the post-approval phase.[5,6,8]

Increased utilization of postmarketing data

Postmarketing studies should be adequately controlled and well timed. Postmarketing trials would ensure that a larger database of patients is studied under realistic trial conditions, and the results would be more representative of patients with the infectious disease under study. Approval can be withdrawn for a number of reasons including the failure of the postmarketing clinical study to prove or verify the clinical efficacy and safety or if the drug is not safe under its conditions of use.[8]

Designation of orphan drug status for antibiotics

It should be noted that the Orphan Drug (OD) Act offers protection against competition by conferring exclusive marketing rights. In addition, this act gives tax incentives, grant support for specific clinical development processes, and other benefits for sponsors of drug development for rare diseases. Assignment of OD status for antibiotics that can be used in life-threatening infections coupled with regulatory benefits can spur the research and development of novel antibacterial drugs.[4]

Provisional approval might be given to novel antibacterial drugs based on well-validated phase II data under the OD route, which is more rapid. This approach is well-accepted in cancer research. In addition, accelerated provisional approval of a drug against anthrax employed surrogate data because of the absence of human models. Medicines approved via the

OD route would receive a significant market share, with an advantage of 7 years of market protection.[5]

Accelerating the publication of updated guidelines for antibiotic clinical trials

The publication of updated guidelines for antibiotic clinical trials should be accelerated to ensure that their relevance is preserved.[5-7]

Increased use of PK/PD data

PK/PD data can now be used to determine the dosing regimen. When it is difficult to conduct large trials, PK/PD data can be used for efficacy evaluation. Integration of PK/PD parameters with the minimum inhibitory concentration (MIC) affords 3 measures for predicting antibiotic efficacy, including the peak/MIC ratio, the time that the drug concentration persists above MIC (T > MIC), and the 24-h area under the curve (AUC)/MIC ratio. Various outcome studies have reported that class-appropriate PK/PD parameters are excellent predictors of antibiotic efficacy. Thus, concrete PK/PD data would reduce the need for phase III trials to one trial per indication.[5,6,12,13]

Fostering translational (bench to bedside) research

Translation research involves 2 stages. The first stage is the translation of basic and preclinical data to human clinical data, and the second stage involves the adoption of best practices.[6,7]

Use of surrogate end points

A very large sample size of up to 300 evaluable patients per treatment group is required in clinical trials of anti-infective drugs because efficacy is registered as the number of cured/improved patients versus number of patients in whom the treatment failed. A solution to this problem would be to use validated surrogate markers as end points. Regulatory bodies may provide valid definitions of well-accepted surrogate end points for clinical trials of bacterial infections.[5-7]

Encouraging the development of rapid diagnostics

There is a clear need for the development of rapid diagnostics to simplify both medical practice and drug development. Better diagnostics will not only enable the enrolment of patients with genuine bacterial infections in clinical trials but also simplify the trial design and better the outcome measures.[5-7]

Recent developments

In a recent development, Safety and Innovation Act of the US FDA revised the PDUFA in September 2012 to include incentives to foster the research of antibiotic and antifungal drugs. This law has recognized the need for government intervention to address the serious problems of antibiotic resistance and a sparse antibiotic pipeline.[14] Selected provisions of this law are described in the following section.

Incentives for drugs used for treating serious and life-threatening infections

A list of qualifying pathogens should be prepared. Once a drug qualifies to receive incentives, such a designation remains irrevocable.[14]

Additional exclusivity

Five additional years of data exclusivity for new antibiotics and antifungals have been provided under this act.[14]

Priority review process

Priority review will reduce the time it takes to review a new drug application to 6 months. Qualifying drug candidates will be eligible for review under this law.[14]

CONCLUSIONS

The antibacterial pipeline is scarce because of the costs associated with the development and licensure of antibiotics and complexity of conducting clinical trials involving antibiotics. Clinical trials for novel antibacterials are faced with multiple regulatory bottlenecks. Some regulatory issues include increased stringency of trial design, increased demands regarding the design of phase III studies, necessity for all licensed indications to be microbiologically documented, and increased stringency of safety requirements for pre-licensing and post-licensing procedures of drugs. Some of the measures suggested by the US FDA and other health organizations to spur the research and development of novel antibacterials are appropriate use of imaginative clinical trial designs, increased use of postmarketing studies, designation of OD status, acceleration of the publication of updated guidelines, increased use of PK/PD data, aggressive encouragement of translational research, appropriate use of surrogate markers, development of rapid diagnostics, and a quick review process.

REFERENCES

1. Talbot GH, Bradley J, Edwards Jr JE, Gilbert D, Scheld M, Bartlett JG. Bad bugs need drugs: An update on the development pipeline from the Antimicrobial Availability Task Force of the Infectious Diseases Society of America. Clin. Infect. Dis 2006. 42:657-68.
2. Charles PG, Grayson ML. The dearth of new antibiotic development: Why we should be worried and what we can do about it. Med J Aust 2004;181:549-53.
3. Gupta SK. Non-inferiority clinical trials: Practical issues and current regulatory perspective. Indian J Pharmacol. 2011;43:371-4.
4. Alvan G, Edlund C, Heddini A. The global need for effective antibiotics: A summary of plenary presentations. Drug Resist Update 2011;14:70-6.
5. Report of the British Society for Antimicrobial Chemotherapy Initiative. The Urgent Need, 2011. Regenerating antibacterial drug discovery development. Downloaded from http://www.antibiotic-action.com/wp-content/uploads/2011/07/TUN-Report.pdf. [Last accessed on 2012 Nov 11].
6. Infectious Diseases Society of America. Bad Bugs, No Drugs. As Antibiotic Discovery Stagnates, A Public Health Crisis Brews, July 2004. Downloaded from http://www.idsociety.org/uploadedFiles/IDSA/Policy_and_Advocacy/Current_Topics_and_Issues/Antimicrobial_Resistance/10×20/Images/Bad%20Bugs%20no%20Drugs.pdf. [Last accessed on 2012 Nov 1].

7. US Food and Drug Administration. Innovation or Stagnation: Critical Path Opportunities Report and List, March 2006. Downloaded from http://www.fda.gov/downloads/ScienceResearch/SpecialTopics/CriticalPathInitiative/CriticalPathOpportunitiesReports/UCM077254.pdf. [Last accessed on 2012 Oct 30].
8. California Healthcare Institute. Promoting Antibiotic Discovery and Development, A California Healthcare Institute Initiative, 2012. http://www.chi.org/uploadedFiles/Industry_at_a_glance/CHI%20Antibiotic%20White%20Paper_FINAL.pdf. [Last accessed on 2012 Jul 14].
9. Finch R. Regulatory opportunities to encourage technology solutions to antibacterial drug resistance. J Antimicrob Chemother. 2011;66:1945-7.
10. U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER) Center for Biologics Evaluation and Research (CBER). Guidance for Industry. Non-Inferiority Clinical Trials. March 2010.
11. International Conference on Harmonisation. Guidance E10: Choice of Control Group and Related Issues in Clinical Trials, July 2000.
12. Hyatt JM, McKinnon PS, Zimmer GS, Schentag JJ. The importance of pharmacokinetic pharmacodynamic surrogate markers to outcome. Clin Pharmacokinet. 1995;28:143-60.
13. Ambrose PG, *et al*. Pharmacodynamics of fluoroquinolones against Streptococcus pneumoniae. Antimicrob Agents Chemother. 2001;45:2793-7.
14. Food and Drug Administration (FDA) Safety and Innovation Act Antibiotic Incentives. Created by IDSA. September 7, 2012. Downloaded from http://www.idsociety.org/uploadedFiles/IDSA/Policy_and_Advocacy/Current_Topics_and_Issues/Antimicrobial_Resistance/10×20/Letters/To_Congress/IDSA%20Summary%20of%20Antibiotic%20Incentives%20in%20FDASIA.pdf. [Last accessed on 2012 Nov 11].

How to cite this article: Gupta SK, Nayak RP. Dry antibiotic pipeline: Regulatory bottlenecks and regulatory reforms. J Pharmacol Pharmacother 2014;5:4-7.

Source of Support: Nil, **Conflict of Interest:** None declared.